Physiologically-Based Pharmacokinetic Modeling Combined with Swiss HIV Cohort Study Data Supports No Dose Adjustment of Bictegravir in Elderly Individuals Living With HIV

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Clinical studies in aging people living with HIV (PLWH) are sparse for the novel integrase inhibitor bictegravir, leading to some uncertainty about dosing recommendations for elderly PLWH. The objective of this study was to investigate the continuous impact of aging on bictegravir pharmacokinetics by combining clinically observed data with modeling to support a safe and efficient anti-HIV therapy with advanced age. A physiologically-based pharmacokinetic (PBPK) model was developed for bictegravir with clinically observed data from phase I studies. The predictive model performance was verified using bictegravir plasma concentrations sampled as part of the general therapeutic drug monitoring (TDM) program of the Swiss HIV Cohort Study in young (20–55 years) and elderly PLWH (55–85 years). The verified PBPK model subsequently predicted the continuous impact of aging on bictegravir pharmacokinetics across adulthood (20–99 years). Bictegravir exposure was unchanged in elderly compared with young PLWH when analyzing the TDM data of the Swiss HIV Cohort Study. PBPK simulations predicted clinically observed data from 60 young and 32 elderly PLWH mostly within the 95% confidence interval, demonstrating the predictive power of the used modeling approach. Simulations predicted drug exposure to increase up to 40% during adulthood, which was not statistically significantly different from the age-related pharmacokinetic changes of other HIV and non-HIV drugs. Sex had no impact on the age-related changes of bictegravir pharmacokinetics. Considering the safety margin of bictegravir, a dose adjustment for the novel integrase inhibitor is *a priori* not necessary in elderly PLWH in the absence of severe comorbidities.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ People living with HIV (PLWH) have a similar life expectancy compared with the general population. However, elderly PLWH are often excluded from clinical studies leading to limited knowledge about the continuous impact of aging on drug pharmacokinetics, especially for novel drugs, such as the integrase inhibitor bictegravir.

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ Clinically observed data combined with modeling and simulation was used to analyze bictegravir pharmacokinetics across adulthood to investigate if a dose adjustment based on the age of the treated PLWH would be necessary.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ Bictegravir exposure increases by maximal 40% across adulthood, which is of no clinical relevance considering the large safety margin of bictegravir.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ Dose adjustment of bictegravir based on the age of the treated male and female PLWH are *a priori* not necessary in the absence of severe comorbidities.

Bictegravir, a novel integrase inhibitor against HIV, was approved in 2018 in the United States and Europe.[1,2] The US and European HIV guidelines recommend the combination of bictegravir, tenofovir alafenamide, and emtricitabine (tradename: Biktarvy) as an initial treatment for most people living with HIV (PLWH).[3,4] Bictegravir is metabolized equally by CYP3A and UGT1A1, has

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no inhibitory or inducing potential, and is well tolerated.[5,6] Thus, bictegravir would be well-suited for aging PLWH; however, it is mostly uncertain if bictegravir pharmacokinetics change to a clinically relevant extend to justify a dose adjustment based on the age of the treated individual.

Physiological and biological changes characterize the aging process, which alter drug pharmacokinetics. The most significant changes with aging are the decline in hepatic and renal blood flow and glomerular filtration rate, which result in reduced drug clearance.[7,8] The activity of metabolizing enzymes and active drug transporters appear to remain unchanged in elderly compared with young individuals.[7,9]

Physiologically-based pharmacokinetic (PBPK) modeling is an accepted approach by the regulatory authorities to investigate clinical scenarios that cannot easily or ethically be studied.[10,11] Virtual populations inform the PBPK model, which are based on measured organ weights, regional blood flows, and other physiological parameters important to predict drug pharmacokinetics.[7] A combination of measured *in vitro* and clinically observed *in vivo* data are used to simulate drug disposition in virtual individuals.[12] Simulation results are compared against clinically observed data to verify the developed model before extrapolating to unknown scenarios of interest.

The aim of the present study was to analyze bictegravir pharmacokinetics in aging PLWH ≥ 55 years using our previously developed PBPK model[12] and to verify bictegravir simulations with therapeutic drug monitoring (TDM) data from PLWH enrolled in the Swiss HIV Cohort Study (SHCS).

METHODS

We took three different steps to investigate the impact of advanced age on bictegravir pharmacokinetics. First, we developed a predictive PBPK model for bictegravir using clinically observed data from phase I studies. Second, we verified the model and the extrapolation to the elderly with bictegravir TDM data obtained in young (20–55 years) and elderly PLWH (55–85 years) enrolled in the SHCS. Third, we analyzed the continuous impact of aging (20–99 years) on bictegravir pharmacokinetics.

Physiologically-based pharmacokinetic model

A whole-body PBPK model constructed in Matlab 2017a was used. The structure of the PBPK model contained 18 compartments, which represent different organs and tissues of the human body.[12] In brief, drug absorption is modeled by a modified version of the compartmental absorption and transit model, using *in vitro* permeability data from Caco-2 cells as the main input. A limitation is that complex formulations and dissolution cannot be simulated.[13] Drug distribution is calculated based on Rodgers and Rowland from the physicochemical properties of a drug.[14–16] Metabolism is accounted for in the intestine and in the liver.[12] Virtual individuals aged 20 to 99 years were created considering age-related demographical (e.g., body weight), physiological (e.g., blood flows), and biological (e.g., metabolizing enzyme activity) parameters with random variability based on normal distribution.[7]

Input parameters for bictegravir were taken from the published literature (**Table S1**). The clearance for each elimination pathway was retrogradely calculated from the clinically observed clearance of 50 mg bictegravir and the known *in vitro* fractions of each elimination pathway.[5,6] Bictegravir is equally metabolized to 90% by CYP3A and UGT1A1, one percent is cleared renally,[17] and the missing clearance was assigned to an unspecified hepatic elimination pathway.

Bictegravir pharmacokinetics were first simulated in young healthy individuals who received single and multiple oral doses of bictegravir (single agent tablet) ranging from 5 to 600 mg.[6] Second, bictegravir plasma concentrations were predicted in young PLWH aged 20 to 55 years, who received 50 mg of bictegravir. Third, bictegravir disposition after 50 mg of bictegravir was simulated in subjects aged 55 to 85 years without modifying any drug parameters. Predictions were judged to be successful if clinically observed data were within the 95% confidence interval of model predictions. Pharmacokinetic parameters (peak concentration (C_{max}), area under the curve to tau (AUC_t), total apparent clearance, volume of distribution (VdF), and elimination terminal half-life ($t_{1/2}$)) had to be predicted within twofold of the clinically observed data, which is considered to be best practice by the regulatory agencies.[18] Model verification of pharmacokinetic parameters is reported as arithmetic mean ± SD. Dose and dosing regimens in the simulations were similar to the conducted clinical studies. We simulated 10 trials containing 10 virtual individuals in each case.

Clinical data for model verification

The bictegravir PBPK model was verified using bictegravir TDM measurements performed in the framework of the SHCS follow-up visits for PLWH aged 20 to 85 years. The time interval between bictegravir intake and blood sampling as well as concomitant non-HIV medications were documented for each TDM sample. Bictegravir concentrations were measured at unselected times after the last drug intake.

All plasma concentrations were measured in the Laboratory of Clinical Pharmacology at the University Hospital of Lausanne. Blood samples were collected and centrifuged in EDTA-containing tubes. Plasma was aliquoted and stored at −80°C until analysis by a validated liquid chromatography coupled to tandem mass spectrometry.[19]

Measured bictegravir concentrations were combined within defined time intervals (0–2 hours, 2–4 hours, 4–6 hours, 6–8 hours, 8–12 hours, 12–16 hours, 16–20 hours, and 20–24 hours) to obtain a noncompartmental approximation of pharmacokinetic parameters in Matlab 2017a for young PLWH aged 20 to 55 years and elderly PLWH aged 55 to 85 years.

Extrapolating bictegravir pharmacokinetics across adulthood

The verified bictegravir PBPK model was used to predict the continuous impact of aging on bictegravir pharmacokinetics after 7 oral doses of 50 mg. Analyzed pharmacokinetic parameters (C_{max}, time to C_{max} (T_{max}), AUC_t, total apparent clearance, VdF, and $t_{1/2}$) were predicted across adulthood (20–99 years) in 500 virtual individuals (50% women) per 5 years and normalized to the youngest age group (20–24 years). The analysis was done for men and women to investigate whether sex has an impact on the age-related changes of bictegravir pharmacokinetics. The results were compared with our previous analysis for non-HIV and other HIV drugs.[8,20] Slopes were statistically compared by a *t*-test for each investigated pharmacokinetic parameter. Results are given as mean (95% confidence interval (CI)).

RESULTS

Bictegravir TDM data were collected for 60 young PLWH with a mean age of 42.2 years (22.8–54.7 years) and 32 elderly PLWH with a mean age of 63.8 years (55.0–81.1 years). All subjects received 50 mg of bictegravir and no inhibitor or inducer of CYP3A and UGT1A1. An approximation of pharmacokinetic parameters from the TDM measurements can be found in **Table 1**. Estimated C_{max} and AUC_t were similar in young and elderly PLWH (ratio elderly/young: 1.04 and 1.01, respectively). In contrast, $t_{1/2}$ increased by 80% in the elderly compared with the young studied group; however, the correct determination of the terminal elimination phase would require a drug cessation.

Table 1 Pharmacokinetic parameters for bictegravir observed in young (20 to 55 years) and elderly (55 to 85 years) PLWH, who participate in the SHCS and predicted by our PBPK model

	C_{max}, ng*h/mL			AUC_t, ng*h/mL			CL/F, L/h			VdF, L			$t_{1/2}$ [h]		
	Observed	Predicted	Ratio p/o	Observed	Predicted	Ratio p/o	Observed	Predicted	Ratio p/o	Observed	Predicted	Ratio p/o	Observed	Predicted	Ratio p/o
Young	5,526 ± 975	4,626 ± 3,208	0.84	80,394 ± 20,970	79,703 ± 76,782	0.99	0.622 ± 0.162	0.627 ± 0.451	1.01	9.9 ± 2.6	11.9 ± 3.8	1.21	20.6 ± 5.4	18.9 ± 11.4	0.91
Elderly	5,745 ± 1,415	4,971 ± 1,988	0.87	80,920 ± 19,928	89,423 ± 46,802	1.11	0.618 ± 0.152	0.559 ± 0.451	0.89	10.8 ± 2.7	10.8 ± 3.5	1.00	37.2 ± 9.2	27.9 ± 15.0	0.75
Ratio elderly/young	1.04	1.07	1.03	1.01	1.12	1.11	0.99	0.89	0.90	1.10	0.90	0.82	1.80	1.48	0.82

AUC_t, area under the curve to tau; CL/F, clearance; C_{max}, peak concentration; PBPK, physiologically-based pharmacokinetic; PLWH, people living with HIV; SHCS, Swiss HIV Cohort Study; $t_{1/2}$, elimination terminal half-life; VdF, volume of distribution.

Development of the bictegravir PBPK model

Clinically observed data in phase I studies conducted in healthy volunteers for single and multiple once daily bictegravir dosing (25 mg, 50 mg, 75 mg, 100 mg, and 300 mg) were mostly contained within the 95% CI of the model predictions (**Figure S1**). C_{max} appeared to be underpredicted, but the predicted and observed mean plasma concentrations for the terminal elimination phases overlaid each other. Plasma concentrations of the 5 mg dosing regimens (single and once daily) were mostly underpredicted apart from the terminal elimination phase after a 5 mg single dose of bictegravir. In contrast, the plasma concentration of the 600 mg single dose was mostly overpredicted. Predicted pharmacokinetic parameters were up to 51.3% within 1.25-fold, up to 76.9% within 1.5-fold, and up to 94.9% within 2.0-fold of clinically observed data (**Table S2**). The ratio predicted:observed for all investigated dosing regimens was 0.84 (95% CI 0.43–1.43) for C_{max}, 0.96 (95% CI 0.55–1.64) for AUC_t, and 1.09 (95% CI 0.95–1.25) for $t_{1/2}$. C_{max} and AUC_t were underpredicted for 5 to 100 mg with the largest underprediction for the 5 mg dosing regimens and overpredicted for 300 and 600 mg.

Verification of the bictegravir PBPK model

TDM concentrations of young and aging PLWH were mostly predicted within the 95% CI of the PBPK model simulations (**Figure 1**). Pharmacokinetic parameters of young and elderly PLWH were all predicted within 1.25-fold of clinically observed data apart from the $t_{1/2}$ in the elderly, which was underpredicted (ratio predicted:observed: 0.75). C_{max}, AUC_t, and $t_{1/2}$ were simulated to increase by 7% (ratio predicted:observed: 1.03), 11% (ratio predicted:observed: 1.11), and 48% (ratio predicted:observed: 0.82), respectively (**Table 1**).

Extrapolation of bictegravir pharmacokinetics across adulthood

C_{max} raised by 0.31% (95% CI 0.24–0.37%) per year, leading to a maximal 25% increase in the oldest compared with the youngest studied age group (**Figure S2**). T_{max} and VdF were unchanged with advanced age. AUC_t and $t_{1/2}$ increased by 0.47% (95% CI 0.40–0.54%) and by 0.61% (95% CI 0.56–0.66%) per year, respectively, which means drug exposure of bictegravir can be increased by up to 40% in the elderly (**Figure 1**). The age-dependent changes for all investigated pharmacokinetic parameters of bictegravir were independent of sex (**Table S3**). Predicted changes of bictegravir pharmacokinetics were in a similar range as for other HIV and non-HIV drugs (**Table S4**).[8,20]

DISCUSSION

Uncertainty exists whether the dose of the novel integrase inhibitor bictegravir would need to be adjusted based on the age of the treated individual.

Our clinical data demonstrated an unchanged drug exposure in the elderly compared with the young PLWH group, which confirms sparse clinical data mentioned in the Biktarvy label.[5] The exposure of other anti-HIV drugs, such as dolutegravir, were also demonstrated to be unchanged with advanced age.[20] However,

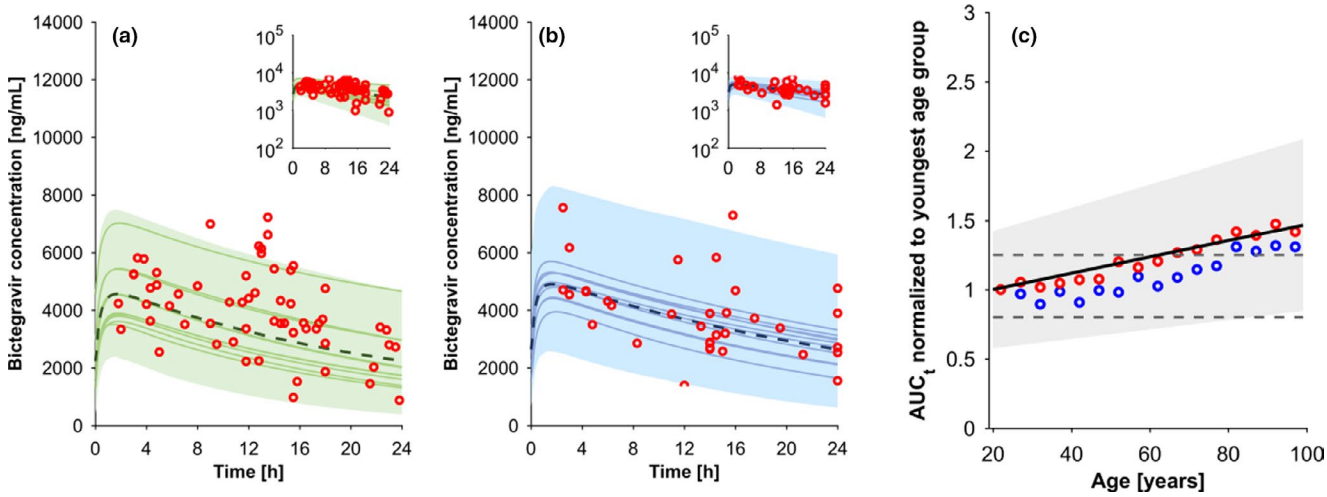

Figure 1 Predicted vs. observed concentration-time profiles for bictegravir in adults aged 20 to 55 years (**a**; green) and in adults aged 55 to 85 years (**b**; blue). Red markers show the clinically observed data from people living with HIV, who participated in the Swiss HIV Cohort Study. Each circle represents an individual sample. The solid lines, the dashed line, and the shaded area represent the mean of each virtual trial (10 trials with 10 individuals in each), the mean, and the 95% confidence interval of the entire virtual population (100 individuals). (**c**) Shows the predicted increase of the area under the curve to tau (AUC_t) for bictegravir in men (blue circles) and women (red circles). The solid line and the grey shaded area display the fitted mean and the estimated variability of age-related pharmacokinetic changes obtained from non-HIV drugs.[8] The grey dashed lines represent the 1.25-fold interval (bioequivalence criterion). [Colour figure can be viewed at wileyonlinelibrary.com]

one general limitation of clinical studies in the elderly is that usually two age groups (young vs. elderly) are compared, but aging is a continuous process.[7] Longitudinal data with each subject as an own control would be necessary, which is not practical or feasible. We used a verified PBPK modeling approach to overcome these hurdles, for which the predictive performance was verified with clinically observed data from the SHCS.

Clinically observed data of bictegravir were generally within the 95% CI except for dosing regimens with 5 mg and 600 mg. The underprediction and overprediction of C_{max} at different doses can be explained by nonlinear absorption process,[6] which was not implemented into the model due to a lack of available *in vitro* data. Only empirical simulations would be possible, which is against the primary aim of this work to predict bictegravir pharmacokinetics with advanced age. As it can be seen from **Table S2**, the model predicts dose-escalation of bictegravir between 25 and 300 mg within 1.5-fold of clinically observed data, which was judged sufficient to scale the model to the elderly. Furthermore, the dose does not change in elderly individuals to below 25 mg or above 300 mg, so that age-related changes in the nonlinearity of the absorption of bictegravir will likely not play a role. Importantly, our bictegravir model predicted the interindividual variability of bictegravir concentration in young and elderly PLWH within the 95% CI (**Figure 1**) and thus, the model performance was considered appropriate to predict the continuous effect of advanced aging on bictegravir pharmacokinetics.

Clearance drives the age-related pharmacokinetic changes of drugs. The reduction in clearance with advanced age is caused by a decrease in hepatic and renal blood flow and in the glomerular filtration rate but was found to be independent of drug characteristics.[8] Bictegravir supports this hypothesis with a predicted clearance decrease by maximal 75%, which is in the same range as for other low-extraction drugs, such as warfarin and tolbutamide.[21,22] The relative age-related physiological changes (e.g., of the hepatic blood flow) are similar for men and women,[7] explaining why age-related pharmacokinetic changes of bictegravir were independent of sex. Bictegravir pharmacokinetics were not shown to be different in men and women.[5] Drug-drug interaction studies with bictegravir showed that a 2.4-fold increase can be well tolerated.[5] Thus, age-related changes in bictegravir exposure can be considered as nonclinically relevant and do not warrant a dose adjustment in elderly PLWH in the absence of severe comorbidities.

With the developed bictegravir model we could only verify in PLWH up to the age of 85 years and thus, simulation results at older ages need to be viewed with caution. Our included elderly PLWH had a declined glomerular filtration rate, common comorbidities (e.g., hypertension), but no severe conditions, such as heart failure classified as New York Heart Association (NYHA) 3 to 4. Therefore, results of our bictegravir study might not be applicable to elderly PLWH with severe diseases. However, it was shown in the French HIV Cohort that 75% of PLWH at least 75 years were non-frail, demonstrating that our study might be representative for the majority of PLWH.[23] Clinical studies investigating the combined effects of aging and severe comorbidities are warranted in the future.

In conclusion, age-related pharmacokinetic changes of bictegravir are not clinically relevant considering the safety margin of the novel integrase inhibitor. Dose adjustment is *a priori* not necessary for bictegravir in elderly PLWH in the absence of severe comorbidities.

SUPPORTING INFORMATION

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (www.cpt-journal.com).

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AUTHOR CONTRIBUTIONS

F.S. wrote the manuscript. F.S. and C.M. designed the research. F.S. and P.C. performed the research. F.S., M.B., L.A.D., and C.M. analyzed the data.

CONFLICT OF INTEREST

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